

REMARKS

Claims 74-92 are pending and under examination. Applicants have hereinabove amended claim 74. Support for the amendments to claim 74 can be found in Figure 12, and in the specification as originally filed at, *inter alia*, page 32, lines 11 to 23. Accordingly, applicants respectfully request entry of this amendment. In view of the amendments made herein and the remarks below, applicants respectfully request that the Examiner's objections and rejections be withdrawn.

Objection to the Specification

The Examiner stated that the specification is objected to as documents have been improperly incorporated by reference. The Examiner stated that the specification states "Throughout this application, various publications are referenced in parentheses by author and year. Full citations for these references may be found at the end of the specification immediately preceding the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains." The Examiner further stated that such omnibus language fails to specify what specific information applicant seeks to incorporate by reference and similarly fails to teach with detailed particularity just where that specific information is to be found in each of the cited documents and that, accordingly, the cited documents are not considered to have been properly incorporated by reference.

In response, applicants note that, because the references have

been incorporated in order to explain the state of the art, the entire disclosure of each reference is the pertinent and appropriate incorporated portion. Accordingly, applicants maintain that the cited references are properly incorporated and respectfully request that the Examiner reconsider and withdraw this objection.

Rejection of Claims Under 35 U.S.C. §112 (Written Description)

The Examiner stated that claims 74-92 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner further stated that claim 74 has been interpreted as encompassing determining the difference in molecular weight between different labeled DNA sequencing fragments via mass spectrometry, where the DNA sequencing fragments have not been further manipulated or modified since passage through the channel(s) and well(s). The Examiner further stated that, to that end, the claimed method fairly encompasses practicing a method where the samples are not free from alkaline or alkaline-earth salts, or any other contaminant. The Examiner also stated that the specification, however, cautions artisans "in order to obtain accurate measure of the mass of the sequencing DNA fragments, the samples must be free from alkaline and alkaline-earth salts. Samples must be desalted and free from contaminants before the MS analysis."

In response, applicants respectfully traverse the Examiner's rejection. More particularly, applicants note that the invention disclosed specifically avoids the problems of salt contamination cited by the Examiner. Applicants note that "all other components are washed away" (page 37, lines 15 to 19) in the disclosed

method, and that "salts can ruin spectra", but in the next line of the specification it is noted that "the method disclosed here eliminates all these problems" see page 38, lines 17 to 20. Applicants further note that the specification discloses working examples showing that "clean sequencing ladders that are free from any other contaminants can be obtained", page 39, lines 25-27. Accordingly, applicants assert that the method disclosed specifically avoids the problems of alkaline and alkaline-earth salt contamination by employing an affinity system, and a washing process (see step (d) of claim 74), and that the specification clearly describes this (see page 36, lines 27 to 30, for example). Accordingly, applicants request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner further stated that the claimed method has been interpreted as comprising a plurality of wells connected via a channel, where the channel and wells are within a chip. The Examiner further stated that a review of the disclosure, however, fails to find an adequate written description of such a device, rather, the specification has been found to provide a description via Fig. 12, of two 96-well plates that are connected via glass capillary tubes to corresponding single channels in a chip.

In response, applicants respectfully traverse the Examiner's position. Applicants note that the Examiner is construing the claimed method with the characteristic that the channel and wells "are within a chip". In fact, the claim does not recite such a characteristic, but recites "a system" comprising a plurality of wells and a channel connected at each end to a well (see step (c) of claim 74), and does not recite that the channels and the wells are "within a chip". An example of such a system is illustrated,

and described, in figure 12. In addition, without conceding the correctness of the Examiner's position, but in order to expedite prosecution, applicants have hereinabove amended claim 74 to more clearly recite the claimed invention. Accordingly (and without conceding that a chip, were it claimed, would not be described), applicants maintain that the claimed invention is clearly described in the specification, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner further stated that the device described lacks any means for applying pressure such that any one, much less 96 different samples could be passed through the coated channels in one direction, much less back-and-forth, thereby permitting/enabling the binding of the DNA sequencing fragments.

In response, applicants respectfully traverse the Examiner's position. More particularly, applicants note that moving a liquid through a channel, by gas pressure for example, is a fundamental and notoriously well known technique which applicants maintain would be well known to those of ordinary skill in the art. It is noted that "information which is well known in the art need not be described in detail in the specification", MPEP §2163 (II) (A)(2). Accordingly, applicants maintain that the claimed invention is clearly described in the specification, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner further stated that the claimed method has been interpreted as requiring but a single pass of the sample through the channels, however, page 48, lines 26-29, describes a method requiring pressure to be applied in reverse in order to drive

"the sample through the channel multiple times," thereby ensuring a high efficiency solid phase capture.

In response, applicants respectfully traverse the Examiner's position. More particularly, applicants note that the specification support cited by the Examiner regarding multiple passing of the sample through the channel merely shows how the efficiency of the system can be increased, but that it is not a requisite for the system to function, and as such is not an element of the claims. Accordingly, applicants maintain that the claimed invention is clearly described in the specification, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner stated that the claimed method has also been interpreted as encompassing the simultaneous sequencing of multiple DNA sequencing fragments in a common channel. The Examiner stated that to perform such a maneuver would present situations where multiple signals would be generated at the same time, yet would correspond to the different templates, and that the use of knowingly different DNA fragments will cause situations where the nucleotide sequence is anything but clearly resolvable. The Examiner stated that the specification has not been found to provide an adequate written description of how this issue is to be overcome.

In response, applicants respectfully traverse the Examiner's rejection. Initially, applicants note that the mass resolution of the claimed method is sufficient to distinguish the different fragments by mass spectrometry. In addition, without conceding the correctness of the Examiner's position, but in order to

expedite prosecution, applicants have hereinabove amended claim 74 to more clearly recite the claimed invention. As amended, step (c) of claim 74 makes it clear that the channel is connected at each end to a different well.

The Examiner stated that the claimed method fairly encompasses the use of mass spectrometry in the analysis of the DNA fragments, but that the use of lasers in performing mass spectrometry is recognized in the art as causing significant problems in sequencing. The Examiner stated that in support of this position attention is directed to US Patent Application Publication 2002016842A1, paragraph 13, which states that "Even for a homogenous population of single stranded DNAs, the resultant fragments have a broad range of lower masses. For projected heterogeneous single stranded population as inputs for sequencing, lower mass members will be within the fragmentation background and thus harder to recognize." The Examiner further stated that the specification of the subject application has not been found to provide an adequate written description as to how art-recognized issues are to be overcome.

In response, applicants respectfully traverse the Examiner's position. More particularly, applicants note that the specification clearly demonstrates with working examples the effective use of MALDI TOF mass spectrometry to sequence nucleic acids (see figure 2, and page 38, lines 27 to 31). Moreover, applicants maintain that actual working examples show that the claimed method clearly works notwithstanding "problems" encountered in different methods not claimed here and hypothetically applied to the claimed method.

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Accordingly, applicants maintain that the claimed invention is clearly described in the specification, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection of Claims Under 35 U.S.C. §112 (Enablement)

The Examiner stated that claims 74-92 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner stated that, as presented above, the specification has not been found to provide an adequate written description of the invention to where the specification does not reasonably suggest that applicant did not possess the entire invention at the time of filing, and that it is well settled that one cannot enable that which they do not yet possess. The Examiner also stated that the record clearly shows that the claimed method fairly encompasses embodiments where art-recognized issues of enablement would be encountered, yet the specification is effectively silent as to how they are to be overcome without the skilled artisan resorting to undue experimentation.

In response, applicants respectfully traverse the Examiner's rejection. Applicants have hereinabove pointed out how the claimed invention is fully described in the specification, and since the reasons supporting the enablement rejection are the same as those supporting the written description rejection, these arguments apply to the enablement rejection. Moreover, in response to the Examiner's statement regarding "art-recognized issues of enablement", applicants maintain that the claimed method presented here is demonstrated in the working examples

provided and specifically overcomes various enumerated art problems (noting that the specification states that "the method disclosed here eliminates all these problems", see page 38, lines 17 to 20). Applicants also assert that the physico-chemical nature of the art field is also relatively predictable. Accordingly, applicants maintain that the claimed invention is clearly enabled by the specification, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary

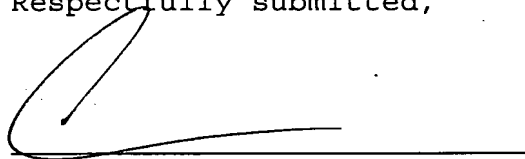
Applicants maintain that the claims pending are in condition for allowance, and accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.


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No fee is deemed necessary in connection with the filing of this Amendment. If any fee is required, however, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450


Alan J. Morrison
Reg. No. 37,399

2/17/04
Date

John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicants
Cooper & Dunham LLP
1185 Ave of the Americas
New York, New York 10036
(212) 278-0400